

NOVEL YLIDIC PHOSPHORYL COMPOUNDS FROM HALOGENATED FURAN-2,5-DIONES WITH TRIVALENT PHOSPHORUS ESTERS: APPLICATION OF THIS APPROACH TO NEW TRISPHOSPHONATES CONTAINING A GEMINAL BISPHOSPHONATE UNIT

D. Vaughan Griffiths,^{a*} David M. Benoit,^b Yuen-Ki Cheong,^a Philip Duncanson,^a and Xiao Han^a

*^a School of Biological and Chemical Sciences, Queen Mary University of London, Mile End Road, London, England, E1 4NS, ^bDepartment of Chemistry, University of Hull, Cottingham Road, Hull, HU6 7RX. *E-mail: d.v.griffiths@qmul.ac.uk*

Shortened title: NOVEL YLIDIC PHOSPHORYL COMPOUNDS

ACKNOWLEDGEMENTS

The authors wish to thank the EPSRC mass spectrometry service at Swansea.

NOVEL YLIDIC PHOSPHORYL COMPOUNDS FROM HALOGENATED FURAN-2,5-DIONES WITH TRIVALENT PHOSPHORUS ESTERS: APPLICATION OF THIS APPROACH TO NEW TRISPHOSPHONATES CONTAINING A GEMINAL BISPHOSPHONATE UNIT

Abstract The reactions of trivalent phosphorus esters, including trialkyl phosphites, dialkyl phosphonites and alkyl phosphinites, with 3-halo- and 3,4-dihalo-furan-2,5-diones has been shown to lead to the formation of novel phosphorus ylides possessing additional phosphoryl-containing groups. For the reaction of 3,4-dihalo-furan-2,5-diones with trialkyl phosphites the products are trialkoxyphosphonium ylides containing an adjacent geminal bisphosphonate unit. These can be used to provide a convenient route to novel 2,3,3-tris(dialkoxylphosphoryl)-substituted propionate esters which can be hydrolysed to give the corresponding novel trisphosphonic monocarboxylic acid.

Keywords halogenated furan-2,5-diones; trivalent phosphorus esters; ylides; geminal bisphosphonates; trisphosphonates

INTRODUCTION

The synthesis of systems containing a geminal bisphosphonate unit has attracted considerable interest because of the ability of some of these systems to bind to the surface of bone or to affect bone metabolism. We have had a long-standing interest in those geminal bisphosphonates that bind to bone in the context of developing radiopharmaceutical agents for both skeletal imaging¹ and therapy.² On the other hand, bisphosphonates that affect bone metabolism can be used to treat bone related disorders such as Paget's disease³ and osteoporosis.⁴

We have therefore maintained an interest in reactions that could be exploited to generate systems containing a geminal bisphosphonate unit. In our studies of the reactions of

trialkyl phosphites with aroyl-⁵ and heteroaroyl-phosphonates,⁶ for example, we have shown that under appropriate conditions the initially produced carbene intermediates can be trapped by phosphite to give novel ylidic phosphonates that can be readily converted into such geminal bisphosphonates.

We have also studied the reaction of 3-halofuran-2,5-diones with trivalent phosphorus esters, including trialkyl phosphites, dialkyl phosphonites and alkyl phosphinites and have observed the unexpected formation of novel ylidic monophosphoryl compounds. This prompted us to investigate whether we could use dihalogenated furan-2,5-diones to extend this approach to prepare analogous ylidic systems containing a geminal bisphosphoryl unit and, in particular, those containing a geminal bisphosphonate unit. In this paper we report our studies of the reaction of trialkyl phosphites and other trivalent phosphorus compounds with both mono- and di-halogenated furan-2,5-diones and show how, by reacting trialkyl phosphites with 3,4-dihalofuran-2,5-diones, we have been able to develop a new routes to some novel systems containing the geminal bisphosphonate unit.

RESULTS AND DISCUSSION

It has been previously reported⁷ that the reaction of secondary phosphines with 3-bromofuran-2,5-dione (bromomaleic anhydride) **1** and related compounds leads to the formation of novel bisphosphines **2** *via* a sequence of addition elimination steps. Similarly, 2,3-bis(diphenylphosphino)furan-2,5-dione **4** was formed in the reaction of 3,4-dichlorofuran-2,5-dione **3** with diphenyl(trimethylsilyl)phosphine (Scheme 1).⁸

“Scheme 1”

We have observed a quite different outcome with the trivalent phosphorus compounds we have studied, which include trialkyl phosphites, dialkyl phosphonites and alkyl phosphinites. Thus, the reaction of trimethyl phosphite with 3-bromofuran-2,5-dione **1** in

dichloromethane at, or slightly below, room temperature led cleanly over a period of about 2 h to the formation of a diphosphorus compound, δ_P 45.2 [P(OMe)₃] and 21.3 [P(O)(OMe)₂], identified as the ylidic phosphonate **7a** (Scheme 2).

“Scheme 2”

The presence of the trimethoxyphosphonium centre in **7a** was indicated by the shift and multiplicity of the proton-coupled phosphorus resonance at δ_P 45.2, while the α -carbon was observed at relatively high field exhibiting a characteristically large coupling to phosphorus⁹ [δ_C 37.0, dd, J_{PC} = 255 and 2 Hz] (*c.f.* that for the carbon adjacent to the phosphonate group [δ_C 45.9, dd, J_{PC} = 142 and 12 Hz]). The corresponding ylidic phosphonates **7b** and **7c** were produced when triethyl and triisopropyl phosphite were used. It is interesting to note that despite their relatively close proximity no visible ^{31}P – ^{31}P coupling was observed between the resonances for the ylide and phosphonate groups in the ^{31}P NMR spectra of these compounds.

Analogous diphosphorus products were produced when dimethyl phenylphosphonite and methyl diphenylphosphinite were used in place of a trialkyl phosphite, these giving the corresponding ylides **7d** [as a diastereoisomeric mixture, δ_P 34.7 (s) and 63.4 (s) (55%); and δ_P 34.6 (s) and 63.3 (s) (45%)] and **7e** [δ_P 24.9 (s) and 50.1 (s)].

In all cases NMR studies showed the formation of the ylides **7a–e** proceeded cleanly and in essentially quantitative yields. These ylides **7a–e** were also sufficiently stable to be chromatographed under appropriate conditions, although some losses were incurred while isolating the analytically pure ylides using this approach.

It is of interest to note that while the formation of these ylides clearly involved more than one step, at no time were products other than the ylides **7a–e** observed in the reaction mixtures, even when the 3-bromofuran-2,5-dione **1** was kept in excess. This indicates that the

phosphorus reagents react more slowly with 3-bromofuran-2,5-dione **1** than any subsequently formed phosphorus intermediate products.

Possible routes for the formation of the ylides **7a–e** are shown in Scheme 2. Route A involves an initial substitution of the halogen by the phosphorus reagent to give the phosphonium systems **5a–e** which must then undergo reaction with a further molecule of the phosphorus reagent before their phosphonium centres are dealkylated to give a phosphoryl group. Dealkylation of the resulting ylidic-phosphonium systems **6a–e** then gives the observed ylidic-phosphoryl systems **7a–e**.

It is interesting to note, however, that DFT calculations (see Supplemental Materials) indicate that the energy barrier to attack by phosphite on the 3-bromofuran-2,5-dione **1** is lower for attack at C-4 than at C-3 by about approximately 10 kJ/mol, which means that Route B shown in Scheme 3 cannot be ruled out as the pathway to the ylidic-phosphoryl systems **7a–e**. In this alternative pathway, nucleophilic attack by the phosphorus compounds at C-4 and subsequent loss of bromide results in the formation of the carbene intermediates **8a–e** which would then be rapidly trapped by a second molecule of the trivalent phosphorus compound to give the ylidic systems **6a–e**, the same ylidic-phosphonium intermediates proposed in Route A. We have observed rapid ylide formation *via* the trapping of carbene intermediates by these same phosphorus reagents in other systems we have studied.^{9,10}

It is interesting to note that while subsequent studies confirmed that the furan-2,5-dione ring was still intact in these ylides, the IR bands associated with the anhydride group in these compounds are at lower wavenumber than in related cyclic anhydrides. Thus, for example, while itaconic anhydride gives two bands in the carbonyl region at *ca* 1780 and 1850 cm⁻¹,¹¹ those in the ylidic phosphonate **7b** were at 1726 and 1794 cm⁻¹, this presumably reflecting some delocalisation of the anionic charge on the ylidic carbon onto the adjacent carbonyl group. Treatment of the ylides **7a–e** with hydrogen chloride resulted in the

formation of the corresponding symmetrical diphosphoryl compounds **9a–e** that exhibited bands in their IR spectra more typical of a cyclic carboxylic anhydride. Thus, for example, **9b** gave two bands in the carbonyl region at 1790 and 1867 cm⁻¹.

In an attempt to obtain evidence for the possible involvement of the carbene intermediates **8**, we studied the reaction of some 4-substituted 3-chlorofuran-2,5-diones, such as **10a** and **10b** (Scheme 3), in the hope that the carbene intermediate might undergo intramolecular insertion into the substituent to give cyclic systems, such as **11a** and **11b**. We have previously successfully used an intramolecular trapping approach in similar circumstances when the trivalent phosphorus component used to generate the carbene also trapped it to the exclusion of other added carbene trapping agents.^{9, 10, 12}

However, no cyclisation was observed when **10a** was heated with triethyl phosphite in toluene and instead, in addition to the expected ylidic phosphonates **12a** (*ca.* 58%), we observed the formation of the corresponding *Z* and *E* isomeric ylides **13a** (*ca.* 27%) and **14a** (*ca.* 15%) (Scheme 3).

“Scheme 3”

A similar outcome was observed when the corresponding phenoxymethyl substituted system **10b** was heated in toluene with triethyl phosphite. This produced a mixture of **13b** (*ca.* 76%), **14b** (*ca.* 17%) and **12b** (*ca.* 7%) although here a greater preference for the formation of the *Z*-isomer **13b** was observed. This preference for the *Z*-isomer was even more marked when the reaction was carried out at room temperature in dichloromethane. Here there was no sign of any significant quantity of the *E*-isomer **14b** although now the major product was not the alkene **13b** (*ca.* 25%) but the ylidic phosphonate **12b** (*ca.* 75%).

The most likely route to the isomeric ylides **13a,b** and **14a,b** is shown in Scheme 3 and does not involve a carbene intermediate. Instead, it appears that the presence of the RCH₂

substituent encourages preferential attack at the halogenated carbon, forming the phosphonium salt intermediates **15a,b**, which then undergoes hydrogen abstraction to give the observed ylides **13a,b** and **14a,b**. Due to the presence of the RCH₂ substituent it is likely that the formation of the ylidic phosphonates **12a,b** also proceeds *via* attack at the halogenated carbon atoms in **10a,b** in a pathway analogous to that shown for Route A in Scheme 2.

Since we were interested to see if a similar approach could be used to develop a route to compounds containing a geminal bisphosphoryl unit we next investigated the reaction of 3,4-dichlorofuran-2,5-dione (dichloromaleic anhydride) **3** with trivalent phosphorus esters including trialkyl phosphites. These reactions proceeded cleanly to give triphosphorus compounds that we were able to identify as the ylidic bisphosphoryl compounds **18a–e** (Scheme 4).

“Scheme 4”

Thus, for example, trimethyl phosphite reacted with 3,4-dichloro-furan-2,5-dione **3** in dichloromethane at room temperature over a period of about 16 h to give the ylidic bisphosphonate **18a**, δ_P 44.6 [s, P(OMe)₃] and 16.3(x2) [s, P(O)(OMe)₂]. As anticipated, the ylidic carbon resonance in this compound [δ_C 42.0 (dt, J_{PC} = 256 and 4 Hz)] was once again observed at unusually high field for an sp² hybridised carbon and exhibited a characteristically large coupling to the adjacent phosphorus atom and longer range coupling to the two phosphonate groups. In comparison, the carbon adjacent to the two phosphonate groups was observed as a large triplet of doublets [δ_C 58.8 (td, J_{PC} = 138 and 14 Hz)]. As with the ylidic monophosphoryl compounds **7** and **12** discussed earlier, no coupling between the phosphorus groups was observed in the ³¹P NMR spectra of the ylidic bisphosphoryl compounds **18a–e**.

NMR monitoring studies showed that, even when the anhydride **3** was kept in excess throughout the reaction, the ylidic-bisphosphoryl compounds **18a–e** were still formed cleanly in essentially quantitative yield with no observation of resonances that could be attributed to phosphorus-containing intermediates on the reaction pathway.

The mechanism proposed to account for the formation of these ylidic-bisphosphoryl compounds **18a–e** (Scheme 4) initially involves the substitution of one of the chlorine atoms by the phosphorus reagent to give the phosphoryl systems **16a–e**. While pathways analogous to both Routes A and B (Scheme 2) could then explain the subsequent formation of **18a–e** from **16a–e**, DFT calculations (see Supplemental Materials) suggest that the presence of the initially introduced phosphorus group would encourage subsequent attack at the remaining chlorinated carbon. This gives the phosphonium-phosphoryl systems **17a–e** which are converted to the observed ylidic-bisphosphonates **18a–e** in a manner analogous to that proposed for the conversion of **5** to **7** (Route A, Scheme 2). However, we were unable to confirm this mechanism since, as previously noted, we were unable to observe the presence of either of the intermediate compounds **16** and **17** by NMR during the reaction. This may, however, simply indicate that their subsequent reaction with phosphorus reagent is faster than their rate of formation.

The ylidic bisphosphoryl compounds **18a–e**, like the ylidic monophosphoryl compounds **7** and **12**, were sufficiently stable to be purified by column chromatography and this also enabled the two diastereomeric forms of the ylide **18d** [(\pm) δ_P 32.9 (d, J_{PP} = 22 Hz), 33.8 (d, J_{PP} = 22 Hz) and 64.1 (s); and *meso* δ_P 34.2 (x2)(s) and 64.1 (s)] to be successfully separated. It is interesting to note that while the non-equivalence of the phosphonate resonances in ^{31}P NMR spectrum of the (\pm)-diastereoisomer of **18d** gives rise to the observation of a $^2J_{PP}$ coupling between them, neither of these resonances show a $^3J_{PP}$ coupling to the ylidic phosphorus atom.

Once again the IR bands associated with the anhydride units in the ylidic bisphosphoryl compounds **18** showed a shift to lower wavenumber relative to the corresponding trisphosphoryl systems **19**. Thus, for example, whereas the ylide **18c** exhibited bands at 1714 and 1790 cm^{-1} the corresponding trisphosphonate **19c**, formed by passing anhydrous HCl into a solution of the ylide in DCM, showed bands at 1781 and 1861 cm^{-1} .

Interestingly, heating the ylides **18a–c** with their corresponding alcohol under reflux led not only to decomposition of the ylide group but also ring opening of the anhydride and subsequent decarboxylation to give the highly phosphorylated propionates **20a–c**. The same products could also be prepared by heating the trisphosphonates **19a–c** with the corresponding alcohol.

Decomposition of the ylidic bisphosphonate **18b** with dry hydrogen chloride followed by subsequent hydrolysis of the ester groups also provided a route to 2,3,3-tris(phosphono)propionic acid **20** ($R = H$). Although attempts to obtain an analytically pure sample of this material proved unsuccessful due to its hygroscopic nature its ^{13}C NMR spectrum confirmed the loss of the ethyl ester groups and the presence of the required carbon skeleton [^{13}C NMR (D_2O , pH 1; ref. 1,4-dioxan at δ_{C} 66.7 ppm) δ : 37.9 (t, $J_{\text{PC}} = 123$ Hz, C-3), 44.6 (d, $J_{\text{PC}} = 116$ Hz, C-2) and 171.4 (s, CO_2H)].

EXPERIMENTAL

General details¹³

NMR spectra were recorded on JEOL EX-270, Bruker AMX400, AV400 and AV600 spectrometers. ^{31}P NMR spectra are referenced to 85% phosphoric acid, ^1H NMR spectra are referenced to TMS, ^{13}C NMR spectra are referenced to CDCl_3 at 77.23 ppm. J values are given in Hz, ' J ' indicates the apparent coupling constant in a second order multiplet. TLC was performed with alumina backed silica gel 60 F₂₅₄ eluting with the solvent system used for

the column chromatography unless otherwise stated and the plates were visualised under UV light or developed in an iodine tank. Column chromatography used silica gel with particle size 33–50 μm and was purchased from BDH. More detailed preparative procedures and additional characterisation data are provided in Supplemental Materials. Details of the computational work carried out and the results obtained are also included in Supplemental Materials.

Typical procedure for the reaction of 3-bromofuran-2,5-dione (1) with the trivalent phosphorus esters

A solution of the appropriate phosphorus ester $\text{R}'\text{R}''\text{POR}$ (10.4 mmol) in dichloromethane (5 mL) was added dropwise, with stirring, to a solution of 3-bromofuran-2,5-dione (860 mg, 5 mmol) in dichloromethane (15 mL), cooled in an ice bath. The cooling bath was then removed and the stirring continued for a further 2 h. Volatile components were removed by warming under reduced pressure to leave the ylide in a good state of purity. A pure sample of the product was obtained by chromatography on Florisil or silica gel eluting with dichloromethane/acetonitrile mixtures.

Dimethyl 2,5-dioxo-4-(trimethoxy- λ^5 -phosphoranylidene)tetrahydrofuran-3-ylphosphonate (7a) (1.05 g, 64%) was isolated as a viscous oil. ^{31}P NMR (109.3 MHz; CDCl_3) δ : 21.3 [s, $\text{P}(\text{O})(\text{OMe})_2$] and 45.25 [s, $\text{P}(\text{OMe})_3$]; ^{13}C NMR (67.9 MHz; CDCl_3) δ : 37.0 (dd, $J_{\text{PC}} = 255$ and 2 Hz, C-4), 45.9 (dd, $J_{\text{PC}} = 142$ and 12 Hz, C-3); IR (film, cm^{-1}) ν : 1790, 1724; HRMS (FAB) m/z 331.0360, ($\text{M}+\text{H}^+$) $\text{C}_9\text{H}_{17}\text{O}_9\text{P}_2$ requires 331.0348.¹³

Diethyl 2,5-dioxo-4-(triethoxy- λ^5 -phosphoranylidene)tetrahydrofuran-3-ylphosphonate (7b) (1.00 g, 50%) was isolated as a viscous oil; ^{31}P NMR (109.3 MHz; CDCl_3) δ : 19.3[s, $\text{P}(\text{O})(\text{OEt})_2$], 40.1[s, $\text{P}(\text{OEt})_3$]; ^{13}C NMR (100.6 MHz; CDCl_3) δ : 36.5 (dd,

$J_{\text{PC}} = 253$ and 4 Hz, C-4), 45.2 (dd, $J_{\text{PC}} = 142$ and 13 Hz, C-3); IR (film, cm^{-1}) ν : 1794, 1726; HRMS (FAB) m/z 401.1139, ($\text{M}+\text{H}^+$) $\text{C}_{14}\text{H}_{27}\text{O}_9\text{P}_2$ requires 401.1130.¹³

Diisopropyl 2,5-dioxo-4-(triisopropoxy- λ^5 -phosphoranylidene)tetrahydrofuran-3-ylphosphonate (7c) (0.53 g, 44%) was isolated as a viscous oil; ^{31}P NMR (109.3 MHz; CDCl_3) δ : 16.0 [s, $\text{P}(\text{O})(\text{O}^i\text{Pr})_2$], 35.0 [s, $\text{P}(\text{O}^i\text{Pr})_3$]; ^{13}C NMR (67.9 MHz; CDCl_3) δ : 39.6 (d, $J_{\text{PC}} = 252$ Hz, C-4), 48.2 (dd, $J_{\text{PC}} = 142$ and 11 Hz, C-3); IR (film, cm^{-1}) ν : 1790, 1720; HRMS (ES) m/z 471.1915, ($\text{M}+\text{H}^+$) $\text{C}_{19}\text{H}_{37}\text{O}_9\text{P}_2$ requires 471.1913..¹³

Methyl [4-(dimethoxyphenyl- λ^5 -phosphanylidene)-2,5-dioxotetrahydrofuran-3-yl](phenyl)phosphinate (7d) was isolated as a oil (505 mg, 60%) containing a mixture of diastereoisomers (A:B 55:45); Isomer A: ^{31}P NMR (109.3 MHz; CDCl_3) δ : 34.7 [s, $\text{P}(\text{O})\text{Ph}(\text{OMe})$] and 63.4 [s, $\text{PPh}(\text{OMe})_2$]; ^{13}C NMR (100.6 MHz; CDCl_3) δ : 39.0 (d, $J_{\text{PC}} = 196$ Hz, C-4), 50.6 (dd, $J_{\text{PC}} = 95$ and 13 Hz, C-3); Isomer B: ^{31}P NMR (109.3 MHz; CDCl_3) δ : 34.6 [s, $\text{P}(\text{O})\text{Ph}(\text{OMe})$] and 63.3 [s, $\text{PPh}(\text{OMe})_2$]; ^{13}C NMR (100.6 MHz; CDCl_3) δ : 39.6 (dd, $J_{\text{PC}} = 197$ and 4 Hz, C-4), 51.3 (dd, $J_{\text{PC}} = 93$ and 13 Hz, C-3).¹³

3-(Diphenylphosphinoyl)-4-(methoxydiphenyl- λ^5 -phosphanylidene)dihydro-furan-2,5-dione (7e) (600 mg, 58%) was isolated as a waxy solid; ^{31}P NMR (109.3 MHz; CDCl_3) δ : 24.9 [s, $\text{P}(\text{O})\text{Ph}_2$] and 50.1 [s, $\text{PPh}_2(\text{OMe})$]; ^{13}C NMR (67.9 MHz; CDCl_3) δ : 41.2 (dd, $J_{\text{PC}} = 152$ and 2 Hz, C-4), 53.7 (dd, $J_{\text{PC}} = 59$ and 10 Hz, C-3); IR (film, cm^{-1}) ν : 1783, 1716; HRMS (ES) m/z 515.1152, ($\text{M}+\text{H}^+$) $\text{C}_{29}\text{H}_{25}\text{O}_5\text{P}_2$ requires 515.1177.¹³

The reaction of 3-benzyl-4-chlorofuran-2,5-dione (10a) with triethyl phosphite

To a boiling solution of 3-benzyl-4-chloro-furan-2,5-dione **10a**¹³ (500 mg, 2.25 mmol) in toluene (20 mL) was added dropwise, over a period of *ca.* 5 min, a solution of triethyl phosphite (750 mg, 4.5 mmol) in toluene (5 mL). After heating under reflux for a further 15

min the mixture was allowed to cool and the volatile components removed under reduced pressure to give a viscous yellow oil which was shown by NMR to contain three ylides, **12a** (58%), **13a** (27%) and **14a** (15%), samples of which were isolated by chromatography on silica gel using a dichloromethane–acetonitrile mixture (1:1) as the eluent.

(Z)-3-Benzylidene-4-(trisethoxy- λ^5 -phosphanylidene)dihydrofuran-2,5-dione

(13a) was isolated as a viscous oil, TLC R_f = 0.75; ^{31}P NMR (109.3 MHz; CDCl_3) δ : 38.3 [s, $\text{P}(\text{OEt})_3$]; ^{13}C NMR (67.9 MHz; CDCl_3) δ : 51.5 (d, J_{PC} = 245 Hz, C-3), 120.4 (s, =CH), 127.1 (d, J_{PC} = 15 Hz, C-4), 167.2 (d, J_{PC} = 26 Hz, C=O) and 168.7 (d, J_{PC} = 26 Hz, C=O); ^1H NMR (270 MHz; CDCl_3) δ : 6.95 (s, 1H, =CH); IR (film, cm^{-1}) ν : 1778, 1720; MS (FAB) m/z 353, ($\text{M}+\text{H}^+$) $\text{C}_{17}\text{H}_{22}\text{O}_6\text{P}$ requires 353.¹³

On exposure to the air this material (**13a**) slowly hydrolysed to give **(E)-3-benzylidene-dihydrofuran-2,5-dione**¹⁴ which was isolated as an oil by chromatography on silica gel using ethyl acetate as the eluent. This material was then crystallised by slow evaporation from a solution in chloroform to give colourless crystals, mp 171–173 °C (lit.,¹⁵ 166–168.5 °C); ^{13}C NMR (100.6 MHz; CDCl_3) δ : 34.1 (CH_2), 119.6 (C-3), 129.6 (x2)(C-3'/5'), 130.8 (x2)(C-2'/6'), 131.7 (C-4'), 133.3 (C-1'), 140.5 (=CH), 166.5 (C-2), 168.6 (C-5); ^1H NMR (400 MHz; CDCl_3) δ : 3.83 (d, J_{HH} = 2.6 Hz, 2H, CH_2), 7.50 ('s', 5H, Ar-H), 7.79 (t, J_{HH} = 2.6 Hz, 1H, =CH); $\nu(\text{KBr})/\text{cm}^{-1}$ 2361, 2355, 1836, 1777, 1651, 1265, 1149, 972; HRMS (FAB) m/z 189.0547, ($\text{M}+\text{H}^+$) $\text{C}_{11}\text{H}_9\text{O}_3$ requires 189.0552.

(E)-3-Benzylidene-4-(trisethoxy- λ^5 -phosphanylidene)dihydrofuran-2,5-dione

(14a) was isolated as a viscous oil, TLC R_f = 0.70; ^{31}P NMR (109.3 MHz; CDCl_3) δ : 39.8 [s, $\text{P}(\text{OEt})_3$]; ^{13}C NMR (67.9 MHz; CDCl_3) δ : 53.6 (d, J_{PC} = 239 Hz, C-3), 123.4 (s, =CH), 127.5 (d, J_{PC} = 14 Hz, C-4), 165.1 (d, J_{PC} = 25 Hz, C=O) and 165.9 (d, J_{PC} = 24 Hz, C=O); ^1H

NMR (270 MHz; CDCl₃) δ : 6.39 (s, 1H, =CH); IR (film, cm⁻¹) ν : 1778, 1720; MS (FAB) m/z 353, (M+H⁺) C₁₇H₂₂O₆P₂ requires 353.¹³

Diethyl 3-benzyl-2,5-dioxo-4-(trisethoxy- λ^5 -phosphanylidene)tetrahydrofuran-3-ylphosphonate (12a) was isolated as a viscous oil, TLC R_f = 0.2; ³¹P NMR (109.3 MHz; CDCl₃) δ : 21.2 [s, P(O)(OEt)₂] and 40.5 [s, P(OEt)₃]; ¹³C NMR (67.9 MHz; CDCl₃) δ : 41.5 (dd, J_{PC} = 248 and 4 Hz, C-4), 58.4 (dd, J_{PC} = 140 and 13 Hz, C-3), 166.4 (dd, J_{PC} = 29 and 6 Hz, C=O) and 173.1 (dd, J_{PC} = 24 and 6 Hz, C=O); ¹H NMR (270 MHz; CDCl₃) δ : 3.01 (dd, J_{HH} = 14 Hz and J_{PH} = 10 Hz, 1H, CHPh), 3.61 (dd, J_{HH} = 14 Hz and J_{PH} = 3 Hz, 1H, CHPh); IR (film, cm⁻¹) ν : 1779, 1721; HRMS (ES) m/z 513.1415, (M+Na⁺) C₂₁H₃₂O₉P₂Na requires 513.1419.¹³

The reaction of 3-chloro-4-(phenoxymethyl)furan-2,5-dione (10b) with triethyl phosphite

1. At 80 °C in toluene

3-Chloro-4-(phenoxymethyl)furan-2,5-dione **10b**¹³ (300 mg, 1.26 mmol) in toluene (2 mL) was added dropwise, over period of *ca.* 5 min, to a solution of triethyl phosphite (500 mg, 3 mmol) in toluene (3 mL) at 80 °C. The mixture was then stirred at 100 °C for 30 min. Volatile components were removed under reduced pressure (40 °C at 15 mmHg) to leave a viscous residue shown to contain the three ylides **13b** (*ca.* 76%), **14b** (*ca.* 17%) **12b** (*ca.* 7%), which was subjected to chromatography on silica gel, using a dichloromethane–acetonitrile mixture (9:1) as the eluant. The first band to be eluted from the column (TLC, R_f = 0.7) was shown to be an isomeric mixture of the 3-phenoxy-methylidene-4-(triethoxy- λ^5 -phosphanylidene)dihydrofuran-2,5-diones **13b** and **14b**. However, further chromatography of this material enabled the pure isomer **13b** to be isolated.

(Z)-3-Phenoxymethylidene-4-(trisethoxy- λ^5 -phosphanylidene)di-hydrofuran-2,5-dione (13b) (250 mg, 54%) was isolated as an oil, TLC R_f = 0.7; ^{31}P NMR (109.3 MHz; CDCl_3) δ : 39.5 [s, $\text{P}(\text{OEt})_3$]; ^{13}C NMR (67.9 MHz; CDCl_3) δ : 48.4 (d, J_{PC} = 249 Hz, C-4), 113.2 (d, J_{PC} = 14.5 Hz, C-3), 136.7 (=CH), 165.1 (d, J_{PC} = 25 Hz, C=O) and 168.1 (d, J_{PC} = 22.8 Hz, C=O); ^1H NMR (270 MHz; CDCl_3) δ : 7.19 (s, 1H, =CH); IR (film, cm^{-1}) ν : 1785, 1719; MS (ES) m/z 369 ($\text{M}+\text{H}^+$, $\text{C}_{17}\text{H}_{22}\text{O}_7\text{P}$ requires 369, HRMS (ES) m/z 759.1941, ($2\text{M}+\text{Na}^+$) $\text{C}_{34}\text{H}_{42}\text{NaO}_{14}\text{P}_2$ requires 759.1947.¹³

Attempts to isolate a pure sample of the corresponding *E*-isomer **14b** were unsuccessful although its ^{31}P and ^{13}C NMR data could be readily obtained from the isomeric mixture.

(E)-3-Phenoxymethylidene-4-(trisethoxy- λ^5 -phosphanylidene)di-hydrofuran-2,5-dione (14b), ^{31}P NMR (109.3 MHz; CDCl_3) δ : 42.8 [s, $\text{P}(\text{OEt})_3$]; ^{13}C NMR (67.9 MHz; CDCl_3) δ : 15.1 (d, J_{PC} = 7.2 Hz, Me), 39.3 (d, J_{PC} = 246 Hz, C-4), 64.5 (x3)(d, J_{PC} = 6 Hz, POCH_2), 113.3 (x2)(C-2'/6'), 113.7 (d, J_{PC} 18.4, C-3), 120.2 (C-4'), 128.5 (x2)(C-3'/5'), 135.7 (=CH), 157.4 (C-1'), 166.0 (d, J_{PC} 27 Hz, C=O) and 173.5 (d, J_{PC} = 23.5 Hz, C=O).

2. At room temperature in dichloromethane

Triethyl phosphite (400 mg, 2.4 mmol) in dichloromethane (1 mL) was added to a solution of 3-chloro-4-phenoxy-methylfuran-2,5-dione **10b** (300 mg, 1.26 mmol) in dichloromethane and the resulting solution stirred at room temperature for 16 h. Volatile components were evaporated under reduced pressure (40 °C at 15 mmHg) to leave a yellow oil that was shown by ^{31}P NMR to contain two ylides, **12b** (*ca.* 75%) and **13b** (*ca.* 25%). This mixture was then subjected to chromatography on silica gel initially using a dichloromethane/acetonitrile (1:1) mixture and then acetonitrile to isolate a sample of the ylidic phosphonate **12b**.

Diethyl 2,5-dioxo-3-phenoxy-methyl-4-(trisethoxy- λ^5 -phosphanylidene)tetrahydrofuran-3-ylphosphonate 12b (310 mg, 48%) was isolated as an oil, TLC R_f = 0.1 (DCM:MeCN

9:1); ^{31}P NMR (109.3 MHz; CDCl_3) δ : 17.8 [s, $\text{P}(\text{O})(\text{OEt})_2$] and 41.3 [s, $\text{P}(\text{OEt})_3$]; ^{13}C NMR (67.9 MHz; CDCl_3) δ : 40.0 (dd, $J_{\text{PC}} = 250$ and 4 Hz, C-4), 58.4 (dd, $J_{\text{PC}} = 143$ and 13 Hz, C-3), 166.8 (dd, $J_{\text{PC}} = 28$ and 5 Hz, C=O) and 171.3 (dd, $J_{\text{PC}} = 23$ and 6 Hz, C=O); IR (film, cm^{-1}) ν : 1793, 1724; MS (ES) m/z 507, $(\text{M}+\text{H}^+)$ $\text{C}_{21}\text{H}_{33}\text{O}_{10}\text{P}_2$ requires 507.¹³

Typical procedure for the reactions of 3,4-dichlorofuran-2,5-dione¹⁶ (**3**) with the trivalent phosphorus ester

A solution of the phosphorus ester $\text{R}'\text{R}''\text{POR}$ (40 mmol) in dichloromethane (5 mL) was added dropwise, over a period of *ca.* 5 min, to a stirred solution of 3,4-dichlorofuran-2,5-dione **3** (13 mmol) in dichloromethane (15 mL) at room temperature. After stirring the mixture overnight, volatile components were removed *in vacuo* (40 °C at 0.005 mmHg) to give the corresponding ylide **18** in a good state of purity. If necessary the ylide **18** can be purified by chromatography on silica gel using dichloromethane–acetonitrile mixtures as the eluant.

Dimethyl 3-(dimethoxyphosphoryl)-2,5-dioxo-4-(trimethoxy- λ^5 -phosphoran-ylidene)-tetrahydrofuran-3-ylphosphonate (18a) (4.4 g, 77%) was isolated in a pure state as a waxy solid; ^{31}P NMR (109.3 MHz; CDCl_3) δ : 16.3 (x2)[s, $\text{P}(\text{O})(\text{OMe})_2$] and 44.6 [s, $\text{P}(\text{OMe})_3$]; ^{13}C NMR (67.9 MHz; CDCl_3) δ : 42.0 (dt, $J_{\text{PC}} = 256$ and 4 Hz, C-4), 58.8 (td, $J_{\text{PC}} = 138$ and 14 Hz, C-3), 165.4 (dt, $J_{\text{PC}} = 21$ and 7 Hz, C=O) and 165.9 (dt, $J_{\text{PC}} = 27$ and 6 Hz, C=O); IR (film, cm^{-1}) ν : 1789, 1723; HRMS (FAB) m/z 439.0330, $(\text{M}+\text{H}^+)$ $\text{C}_{11}\text{H}_{22}\text{O}_{12}\text{P}_3$ requires 439.0324.¹³

Diethyl 3-(diethoxyphosphoryl)-2,5-dioxo-4-(triethoxy- λ^5 -phosphoranylidene)-tetrahydro-furan-3-ylphosphonate (18b) (4.1 g, 62%) was isolated in a pure state as an oil; ^{31}P NMR (109.3 MHz; CDCl_3) δ : 13.9 (x2)[s, $\text{P}(\text{O})(\text{OEt})_2$] and 39.5 [s, $\text{P}(\text{OEt})_3$]; ^{13}C NMR (100.6 MHz; CDCl_3) δ : 43.4 (dt, $J_{\text{PC}} = 253$ and 3 Hz, C-4), 59.6 (td, $J_{\text{PC}} = 136$ and 14 Hz, C-

3), 165.8 (dt, J_{PC} = 21 and 7 Hz, C=O) and 166.6 (dt, J_{PC} = 27 and 6 Hz, C=O); IR (film, cm^{-1}) ν : 1790, 1717; HRMS (FAB) m/z 537.1420, ($M+H^+$) $C_{18}H_{36}O_{12}P_3$ requires 537.1403.¹³

Diisopropyl 3-(diisopropoxyphosphoryl)-2,5-dioxo-4-(tri-isopropoxy- λ^5 -phosphoranylidene)tetrahydrofuran-3-yl-phosphonate (18c) (700 mg, 53%) was isolated in a pure state as an oil; ^{31}P NMR (109.3 MHz; CDCl_3) δ : 11.7 (x2)[s, $\text{P}(\text{O})(\text{OPr}^i)_2$], 34.6 [s, $\text{P}(\text{OPr}^i)_3$]; ^{13}C NMR (67.9 MHz; CDCl_3) δ : 45.3 (d, J_{PC} = 256 Hz, C-4), 60.8 (td, J_{PC} = 138 and 15 Hz, C-3), 166.1 (td, J_{PC} = 21 and 6 Hz, C=O), 167.0 (dt, J_{PC} = 27 and 6 Hz, C=O); IR (film, cm^{-1}) ν : 1790, 1714; HRMS (ES) m/z 657.2293, ($M+\text{Na}^+$) $C_{25}H_{49}\text{NaO}_{12}P_3$ requires 657.2329.¹³

Methyl [4-(dimethoxyphenyl- λ^5 -phosphanylidene)-3-(methoxyphenylphosphinoyl)-2,5-dioxo-tetrahydrofuran-3-yl](phenyl)phosphinate (18d) was prepared as a mixture of diastereoisomers that was separated by chromatography on silica gel eluting with acetonitrile.

The (\pm)-**diastereoisomer** (220 mg 35%) was isolated as a waxy solid; ^{31}P NMR (109.3 MHz; CDCl_3) δ : 32.9 [d, J_{PP} = 22 Hz, $\text{P}(\text{O})\text{Ph}(\text{OMe})$], 33.8 [d, J_{PP} = 22 Hz, $\text{P}(\text{O})\text{Ph}(\text{OMe})$] and 64.1 [s, $\text{PPh}(\text{OMe})_2$]; ^{13}C NMR (100.6 MHz; CDCl_3) δ : 43.2 (ddd, J_{PC} = 197, 5 and 2 Hz, C-4), 65.7 (ddd, J_{PC} = 81, 80 and 9 Hz, C-3), 166.1 (ddd, J_{PC} = 27, 6 and 4 Hz, C=O) and 166.6 (ddd, J_{PC} = 18, 5 and 3 Hz, C=O); IR (film, cm^{-1}) ν : 1778, 1713; MS (ES) m/z 599, ($M+\text{Na}^+$) $C_{26}H_{27}\text{NaO}_9P_3$ requires 599.¹³

The **meso-diastereoisomer** (200 mg, 32%) was isolated as a waxy solid; ^{31}P NMR (109.3 MHz; CDCl_3) δ : 34.2 (x2)[s, $\text{P}(\text{O})\text{Ph}(\text{OMe})$], 64.1 [s, $\text{PPh}(\text{OMe})_2$]; ^{13}C NMR (100.6 MHz; CDCl_3) δ : 43.5 (d, J_{PC} = 197 Hz, C-4), 65.2 (dt, J_{PC} = 85 and 10 Hz, C-3), 165.5 (dt, J_{PC} = 27 and 5 Hz, C=O) and 166.4 (dt, J_{PC} = 18 and 3 Hz, C=O); IR (film, cm^{-1}) ν : 1778, 1714; MS (ES) m/z 599, ($M+\text{Na}^+$) $C_{26}H_{27}\text{NaO}_9P_3$ requires 599.¹³

3,3-Bis-(diphenylphosphinoyl)-4-(methoxydiphenyl- λ^5 -phosphanylidene)-

dihydrofuran-2,5-dione (18e) (1.1 g, 76%) was isolated as a colourless solid; ^{31}P NMR (109.3 MHz; CDCl_3) δ : 24.6 (x2)[s, $\text{P}(\text{O})\text{Ph}_2$] and 61.2 [s, $\text{PPh}_2(\text{OMe})$]; ^{13}C NMR (67.9 MHz; CDCl_3) δ : 45.3 (d, $J_{\text{PC}} = 161$ Hz, C-4), 69.0 (td, $J_{\text{PC}} = 52$ and 8 Hz, C-3), 165.7 (dt, $J_{\text{PC}} = 29$ and 5 Hz, C=O), 169.6 (d, $J_{\text{PC}} = 18$ Hz, C=O); IR (KBr, cm^{-1}) ν : 1766, 1703; HRMS (ES) m/z 737.1354, ($\text{M}+\text{Na}^+$) $\text{C}_{41}\text{H}_{33}\text{O}_6\text{P}_3\text{Na}$ requires 737.1388.¹³

Typical procedure for the decomposition of the ylides 7 and 18 with anhydrous acids

Anhydrous HCl gas was bubbled for 2–3 min into a stirred solution of the ylides **7** or **18** (ca. 1 g) in dichloromethane (10 mL) at room temperature. After a period of 30 min, volatile components were removed under reduced pressure (40 °C at 15 mmHg) to give the corresponding phosphoryl compounds **9** or **19**. If necessary, further purification of compounds **9** can be achieved by chromatography on silica gel using dichloromethane-acetonitrile mixtures as the eluant.

Dimethyl 4-(dimethoxyphosphoryl)-2,5-dioxotetrahydro-furan-3-ylphosphonate

(9a)¹⁶ was isolated as a pale cream coloured solid in essentially quantitative yield; ^{31}P NMR (109.3 MHz; CDCl_3) δ : 18.1; ^{13}C NMR (67.9 MHz; CDCl_3) δ : 42.4 (x2)('dd', ' J_{PC} ' = 141 and 10.4, C-3/4),¹⁷ 164.4 (x2)(br s, C=O).¹³

Diethyl 4-(diethoxyphosphoryl)-2,5-dioxotetrahydrofuran-3-ylphosphonate

(9b)¹⁶ was isolated as a colourless oil (350 mg, 75%); ^{31}P NMR (109.3 MHz; CDCl_3) δ : 15.4; ^{13}C NMR (67.9 MHz; CDCl_3) δ : 44.2 (x2)('dd', ' J_{PC} ' = 141 and 12 Hz, C-3/4),¹⁷ 164.5 (x2)(t, $J_{\text{PC}} = 2$ Hz, C=O); IR (film, cm^{-1}) ν : 1867, 1790; MS (ES) m/z 373 ($\text{M}+\text{H}^+$) $\text{C}_{12}\text{H}_{23}\text{O}_9\text{P}_2$ requires 373.¹³

Diisopropyl 4-(diisopropoxyphosphoryl)-2,5-dioxotetra-hydrofuran-3-ylphosphonate (9c) was produced by reaction of the ylide **7c** with formic acid rather than hydrogen chloride and isolated as an oil (300 mg, 35%), ^{31}P NMR (109.3 MHz; CDCl_3) δ : 13.4; ^{13}C NMR (67.9 MHz; CDCl_3) δ : 44.4 (x2)('dd', ' J_{PC} ' = 142 and 14 Hz, C-3/4),¹⁷ 164.8 (x2)(t, J_{PC} = 2.5 Hz, C=O); IR (film, cm^{-1}) ν : 1867, 1790; MS (ES) m/z 429, ($\text{M}+\text{H}^+$) $\text{C}_{16}\text{H}_{31}\text{O}_9\text{P}_2$ requires 429.¹³

3,4-Bis(diphenylphosphinoyl)dihydrofuran-2,5-dione (9e) was isolated as a colourless solid (110 mg, 44%), ^{31}P NMR (109.3 MHz; CDCl_3) δ : 30.6; ^{13}C NMR (67.9 MHz; CDCl_3) δ : 46.4 (x2)('dd', ' J_{PC} ' = 57 and 9 Hz, C-3/4),¹⁷ 165.6 (x2)(C=O); IR (film, cm^{-1}) ν : 1861, 1790; HRMS (ES) m/z 501.0980, ($\text{M}+\text{H}^+$) $\text{C}_{28}\text{H}_{23}\text{O}_5\text{P}_2$ requires 501.1015.¹³

Dimethyl 3,4-bis(dimethoxyphosphoryl)-2,5-dioxo-tetra-hydrofuran-3-ylphosphonate (19a) was isolated as a colourless oil in essentially quantitative yield, ^{31}P NMR (162 MHz; CDCl_3) δ : 12.1 (d, J_{PP} = 18 Hz, P-3), 15.1 (dd, J_{PP} = 18 and 15 Hz, P-2), 15.2 (s, J_{PP} = 15 Hz, P-1); ^{13}C NMR (67.9 MHz; CDCl_3) δ : 46.9 (dd, J_{PC} = 151 and 4 Hz, C-4), 162.4 (br t, J_{PC} = 10 Hz, C=O) and 163.6 (br d, J_{PC} = 10 Hz, C=O); IR (film, cm^{-1}) ν : 1816, 1790; MS (ES) m/z 423, ($\text{M}+\text{H}^+$) $\text{C}_{10}\text{H}_{18}\text{O}_{12}\text{P}_3$ requires 423.¹³

Diethyl 3,4-bis(diethoxyphosphoryl)-2,5-dioxo-tetrahydro-furan-3-ylphosphonate (19b) was isolated as a colourless oil in essentially quantitative yield, ^{31}P NMR (162 MHz; CDCl_3) δ : 9.6 [dd, J_{PP} = 18.8 and 4.7 Hz, P-3], 12.4 [t, J_{PP} = 18.8 Hz, P-2] and 13.2 [dd, J_{PP} = 18.8 and 4.7 Hz, P-1]; ^{13}C NMR (67.9 MHz; CDCl_3) δ : 48.0 (d, J_{PC} = 143 Hz, C-4), 163.0 (dt, J_{PC} = 9 and 6 Hz, C=O) and 164.3 (td, J_{PC} = 7 and 4 Hz, C=O); IR (film, cm^{-1}) ν : 1860, 1786.¹³

Diisopropyl 3,4-bis(diisopropoxyphosphoryl)-2,5-dioxotetra-hydrofuran-3-ylphosphonate (19c) was isolated as a colourless oil in essentially quantitative yield, ^{31}P NMR

(109.3 MHz; CDCl₃) δ : 8.0 [dd, J_{PP} = 18.8 and 4.7 Hz, P-3], 9.3 [dd, J_{PP} = 35.2 and 18.8 Hz, P-2] and 11.6 [dd, J_{PP} = 35.2 and 4.7 Hz, P-1]; ¹³C NMR (67.9 MHz; CDCl₃) δ : 50.2 (dd, J_{PC} = 135.5 and 3.5 Hz, C-4), 58.1 (dd, J_{PC} = 141 and 116 Hz, C-3), 163.5 (m, C=O) and 164.7 (m, C=O); IR (film, cm⁻¹) ν : 1861, 1781; HRMS (ES) m/z 593.2047, (M+H⁺) C₂₂H₄₄O₁₂P₃ requires 593.2046.¹³

Preparation of the trisphosphonates 20a–c.

Methyl 2,3,3-tris(dimethoxyphosphoryl)propionate (20a)

Method A Methanol (15 mL) was added to the trisphosphonate **19a** and the mixture was stirred for 10 h. Volatile components were then removed under reduced pressure (40 °C at 12 mmHg) to give a residue which was chromatographed on silica gel, eluting with a dichloromethane–methanol (95:9) mixture, to give the pure trisphosphonate **20a** as a pale yellow oil (1.03 g, 73%).

Method B A stirred solution of the ylide **18a** (0.5 g, 1 mmol) in methanol (15 mL) was heated under reflux for 5 h. Volatile components were then removed under reduced pressure (40 °C at 12 mmHg) to give the trisphosphonate **20a** as a pale yellow oil (0.43 g, 92%).

³¹P NMR (242.9 MHz; CDCl₃) δ : 22.3 (d, J_{PP} = 7 Hz, P-3) and 22.8 (dd, J_{PP} = 56 and 7 Hz, P-2) and 23.0 (d, J_{PP} = 56 Hz, P-1); ¹³C NMR (150.9 MHz; CDCl₃) δ : 35.6 (ddd, J_{PC} = 141, 125 and 2 Hz, C-3), 42.8 (ddd, J_{PC} = 130, 5 and 2 Hz, C-2) and 166.8 (m, C=O); IR (film, cm⁻¹) ν : 1755; HRMS (ES) m/z 435.0450, (M+Na⁺) C₁₀H₂₃O₁₁P₃Na requires 435.0351.¹³

Ethyl 2,3,3-tris(diethoxyphosphoryl)propionate (20b)

The ylide **18b** (0.5 g, 0.93 mmol) was heated with ethanol (15 mL) under reflux for 16 h and then evaporated under reduced pressure to give the trisphosphonate **20b** in essentially

quantitative yield. A pure sample of **20b** was isolated using chromatography on silica gel eluting with a dichloromethane/ethanol 9:1 mixture as a pale yellow oil, TLC R_f = 0.62; ^{31}P NMR (109.3 MHz; CDCl_3) δ : 20.9 (d, J_{PC} = 4.5 Hz, P-1), 21.0 (dd, J_{PC} = 55 and 4.5 Hz, P-2) and 21.8 (d, J_{PC} = 55 Hz, P-3); ^{13}C NMR (67.9 MHz; CDCl_3) δ : 36.3 (ddd, J_{PC} = 140, 118 and 7 Hz, C-3), 43.6 (ddd, J_{PC} = 126, 7 and 5 Hz, C-2) and 166.3 (C=O); IR (film, cm^{-1}) ν : 1733; ; HRMS (FAB) m/z 511.1641, ($\text{M}+\text{H}^+$) $\text{C}_{17}\text{H}_{38}\text{O}_{11}\text{P}_3$ requires 511.1627.¹³

Isopropyl 2,3,3-tris(diisopropoxyphosphoryl)propionate (**20c**)

The trisphosphonate **20c** was prepared using Method B by heating the ylide **18c** (3.3 g, 5.2 mmol) with isopropanol (75 mL) under reflux for 5 days. Although this gave the product in a good level of purity a final purification can be achieved if needed by chromatography on silica gel eluting with a dichloromethane–MeOH (95:5) mixture. The pure trisphosphonate **20c** (2.9g, 92%) was isolated as an oil, TLC R_f = 0.45; ^{31}P NMR (109.3 MHz; CDCl_3 ; 60 °C) δ : 18.2 (s, P-2), 19.2 (d, ' J_{PP} ' = 60 Hz, P-3) and 19.9 (d, ' J_{PP} ' = 60 Hz, P-3); ^{13}C NMR (100.6 MHz; CDCl_3) δ : 37.0 (ddd, J_{PC} = 139, 113 and 15 Hz, C-3), 44.0 (ddd, J_{PC} = 112, 13 and 5 Hz, C-2) and 164.8 (t, J_{PC} = 4 Hz, C=O); IR (film, cm^{-1}) ν : 1725; HRMS (ES) m/z 609.2726, ($\text{M}+\text{H}^+$) $\text{C}_{24}\text{H}_{52}\text{O}_{11}\text{P}_3$ requires 609.2717.¹³

2,3,3-Tris(phosphono)propionic acid (**20**; $\text{R} = \text{H}$)

Dry HCl gas was bubbled rapidly into a solution of ylidic bisphosphonate **18b** (0.75 g, 0.14 mmol) in DCM (15 cm^3) for 5 minutes causing the solution to decolourise. After stirring the resulting solution for several minutes the DCM was removed under reduced pressure (30 °C at 12 mmHg) and an acetonitrile/water mixture (20 mL; 1:1) added. The resulting mixture (pH <1) was then stirred for 3 h. The acetonitrile was removed under reduced pressure (30 °C at 12 mmHg) and the residue was partitioned between water (10 cm^3) and dichloromethane (20 cm^3). Removal of the water from the aqueous layer under reduced pressure (70 °C at 12

mmHg) gave a colourless solid (0.16 g, 34%) which was shown by NMR to be the 2,3,3-tris(phosphono)propionic acid **20** (R=H). Attempts to obtain an analytically pure sample of **20** (R=H) were unsuccessful. ^{31}P NMR (161.9 MHz; D₂O, pH 1) δ : 17.1 (dd, J_{PP} = 50 and 12 Hz, P-2), 18.7 (d, J_{PP} 50 Hz, P-3), 19.13 (d, J_{PP} = 12 Hz, P-3); ^1H NMR (400 MHz; D₂O, pH 1; ref. 1,4-dioxan at δ_{H} 3.53) δ : 2.86 (1 H, tdd, J_{PH} = 25 and 12 Hz, J_{HH} = 3 Hz, 3-H), 3.40 (1 H, dddd, J_{PH} = 29.5, 26 and 15 Hz; J_{HH} = 3 Hz, 2-H); ^{13}C NMR (100.63 MHz; D₂O, pH 1; ref. 1,4-dioxan at δ_{C} 66.7) δ : 37.9 (t, J_{PC} = 123 Hz, C-3), 44.6 (d, J_{PC} = 116 Hz, C-2) and 171.4 (s, CO₂H).

CONCLUSIONS

We have shown that the reactions of trivalent phosphorus esters, such as trialkyl phosphites, dialkyl phosphonites and alkyl phosphinites, with 3-halofuran-2,5-diones follow a quite different reaction pathway to that observed when phosphines are used.^{7,8} With the trivalent phosphorus esters the reactions proceeded cleanly with the formation of novel ylides **7** that possess an adjacent phosphoryl-containing group. In the parent 3-bromofuran-2,5-dione **1** case, DFT calculations indicate that there is a lower energy barrier for the initial attack by the phosphorus ester at the C-4 position than at the C-3 position on the ring.¹³ If so, this would suggest the reaction may proceed *via* the carbene mechanism shown in Scheme 2, Route B rather than by an initial substitution of the halogen by the phosphorus reagent (Scheme 2, Route A). On the other hand, when a substituent, such as a benzyl group, is placed on the furan-2,5-dione adjacent to the halogen, as in **10a**, we observe products, such as the benzyldiene-substituted isomers **13** and **14**, which are better explained in terms of an initial attack by the phosphorus ester at the halogenated carbon. This would be consistent with the benzyl substituent inhibiting access to its adjacent carbon by the phosphorus ester.

We have also shown that by starting with 3,4-dihalo-furan-2,5-diones the scope of the reaction can be extended to produce novel ylides **18** that possess an additional geminal bisphosphoryl system. Thus, for example, the use of triethyl phosphite and 3,4-dichlorofuran-2,5-dione **3** gave the novel ylidic bisphosphonate **18b** containing a geminal bisphosphonate unit. Although reactions mechanism analogous to both Routes A and B (Scheme 2) can be drawn to explain the formation of the ylides **18**, DFT calculations¹³ indicate that the presence of the initially introduced phosphorus group in **16** serves to encourage the subsequent attack by the phosphorus ester at the remaining halogenated carbon thus giving the mechanism shown in Scheme 4 rather than one involving a carbene intermediate. The ylidic bisphosphonates **18a–c** have been shown to be valuable precursors for the formation of the corresponding novel trisphosphonates **20a–c** and the trisphosphonic monocarboxylic acid **20**; R = H. Preliminary studies also indicate that the ylidic bisphosphonates **18a–c** will be useful precursors for a range of other highly phosphorylated compounds.

REFERENCES

- 1 (a) Kelly, J. D.; Griffiths, D. V. *Bone seeking complexes of technetium-99m*, PCT Int. Appl. 1988, 20 pp, WO 88/00061; (b) Kelly, J. D.; Griffiths, D. V. *Bone seeking complexes of technetium-99m*, PCT Int. Appl. 1987, 23 pp, WO 87/01289; (c) Griffiths, D. V.; Brown, J. W.; Caesar, J. C.; Cumming, S.A.; Hughes, J. M.; Kelly, J. D.; Swetnam, S. P. *Tetrahedron* **1997**, 53, 17815-17822; (d) Caesar, J. C.; Griffiths, D. V.; Kelly, J. D.; Ruddock, C. F., in Nicolini, M.; Bandoli, G.; Mazzi, U. (eds.) *Technetium in Chemistry and Nuclear Medicine 5*, SGEEditoriali, Padova, 1999, 637-640
- 2 Gibson, A. M.; Mendizabal, M.; Pither, R.; Pullan, S. E.; Griffiths, D. V.; Duncanson, P. *Radiolabelled Bisphosphonates and Method*, Patent WO 01/09146, Feb. 2001, 13 pp.

- 3 Colina, M.; La Corte, R.; De Leonardis, F.; Trotta, F. *Rheumatol. Int.* **2008**, 28(11), 1069-1075.
- 4 Bianchi, G.; Sambrook, P. *Curr. Med. Res. Opin.* **2008**, 24(9), 2669-2677
- 5 Cheong, Y. K.; Duncanson, P.; Griffiths, D. V. *Tetrahedron* **2008**, 64, 2329-2338;
and references cited therein.
- 6 Griffiths, D. V.; Al-Jeboori, M. J.; Cheong, Y. K.; Duncanson, P.; Harris, J. E.; Salt, M. C.; Taylor, H. V. *Org. Biomol. Chem.* **2008**, 6, 577-585 *and references cited therein.*
- 7 van Doorn, J. A.; Frijns, J. H. G.; Meijboom, N. *J. Chem Soc., Perkin Trans. 2*, **1990**, 479-485.
- 8 (a) Fensk, D.; Becher, H. J. *Chem. Ber.* **1975**, 108, 2115-2123; (b) Fenske, D.; Becher, H. J. *Chem. Ber.* **1974**, 107, 117-122; (c) Mao, F.; Tyler, D. R.; Keszler, D. J. *Am. Chem. Soc.* **1989**, 111, 130-134.
- 9 Griffiths, D. V.; Griffiths, P. A.; Whitehead, B. J.; Tebby, J. C. *J. Chem Soc., Perkin Trans. 1* **1992**, 479-484.
- 10 Griffiths, D. V.; Harris, J. E.; Karim, K.; Whitehead, B. J. *Arkivoc* **2000**, 1, 304-311,
and references cited therein.
- 11 Filimoshkin, A. G.; Kosolapova, V. F.; Petrenko, T. V.; Aksenov, V. S.; Poleshchuk, O. Kh. *Russian J. Org. Chem.* **2004**, 40(4), 462-466.
- 12 Griffiths, D. V.; Griffiths, P. A.; Karim, K.; Whitehead, B. J. *J. Chem. Soc., Perkin Trans. 1* **1996**, 555-561.
- 13 Further relevant information available in Supplemental Materials.

- 14 Irradiation of the phenyl resonances in the ^1H NMR spectrum of this isomer resulted in a nuclear Overhauser enhancement of the methylene proton resonance confirming its *E* configuration.
- 15 Horning, E. C.; Walker, G. N. *J. Am. Chem. Soc.* **1952**, 74, 5147-5151.
- 16 Andreae, S.; Pieper, U. *J. Prakt. Chem.* **1994**, 336(1), 75-76.
- 17 Although this resonance at first sight appears to be a doublet of doublets, it has an additional small broad resonance at its centre indicating it is a more complex second order multiplet.